homeostasis comprising a therapeutically effective amount of a hemostatic polymer comprising beads or grains of a crosslinked dextran.

55. A foam product useful for inducing rapid blood coagulation and homeostasis comprising a therapeutically effective amount of a hemostatic polymer comprising beads or grains of a crosslinked dextran.

56. A dressing for inducing rapid blood coagulation and homeostasis comprising a therapeutically effective amount of a hemostatic polymer comprising beads or grains of a crosslinked dextran.

57. A dressing according to claim 56 in the form of a gel.

58. A blood coagulating composition comprising a hemostatic polymer in combination with a pharmaceutically acceptable carrier or diluent, the hemostatic polymer comprising beads or grains of a crosslinked dextran.--

REMARKS

Claims 1-13 and 41 were pending before the Examiner for consideration on the merits, with Claims 14-40 and 42-44 being withdrawn from consideration as allegedly being drawn to a non-elected invention. The Examiner has made formal objections to the specifications and rejected the pending claims under 35 USC § 112, first paragraph, 35 USC § 112, second paragraph, 35 USC § 102 and under 35 USC 103(a). These rejections and the objection are respectfully traversed by Applicants.

A brief, non-limiting summary of the present invention is offered to assist the Examiner's understanding both of the features of the claimed invention and of how these features distinguish the claimed invention from the prior art. The present invention relates to a hemostatic agent or polymer composition comprising beads or grains of a crosslinked dextran which are useful for the rapid induction of blood coagulation and hemostasis at an active bleeding site. The grains or beads absorb low molecular weight (MW) blood and plasma constituents into the grains or beads, while high MW constituents such as fibrinogen, platelets, and clotting factors are concentrated on the surface of the grains or beads. This concentration results in rapid blood coagulation and hemostasis without the use of extraneous or other exogenous compounds.

For the reasons set forth below, Applicants urge that all of the claims in this

application are in condition for allowance and respectfully request issuance of a Notice of Allowance at the earliest possible date.

THE ELECTION/RESTRICTION REQUIREMENT

The election/restriction requirement is respectfully traversed. It is urged that the present invention involves a combination/subcombination situation. With such claims, there must be two-way distinctness for a proper restriction requirement. More specifically, if the particulars of a subcombination are required by the combination, there can be no two-way distinctness. The present invention relates to the Applicants' discovery that beads or grains of crosslinked dextran are useful for stopping bleeding at a bleeding site. All of the present method, composition, and article claims are based on this discovery and all of the claims require the presence of or use of crosslinked dextran beads or grains. Hence, the combination claims require the particulars of the hemostatic agent used.

Applicants respectfully request that the Examiner reconsider and withdraw the restriction requirement. An examination of all of the present claims is further requested.

The Objections to the Specification May Be Properly Withdrawn.

All spelling mistakes and other informalities have been corrected where appropriate. The subject matter objected to as being improperly incorporated by reference is urged to be non-critical subject matter. The instant invention relates to Applicants' discovery of a new use for crosslinked dextran. Crosslinked dextran is not novel in and of itself and is commercially available. The method of preparation is not relevant. It is, however, the new use which allows Applicants to call crosslinked dextran a novel hemostatic agent.

The 35 USC § 112 First Paragraph Rejections of Claims 1-13 and 41 May Properly Be Withdrawn.

The present invention relates to Applicants' discovery that crosslinked dextran beads or grains are useful to stop bleeding at a bleeding site. Crosslinked dextrans, in general, and epicholorohydrin crosslinked dextran are known materials which are commercially available. It is therefore respectfully urged that the present invention

discloses sufficient information in the specification to enable the ordinary artisan to make and use the instant invention.

For these reasons, Applicants respectfully request that the Examiner withdraw the rejection under 35 USC § 112, first paragraph.

The 35 USC § 112, Second Paragraph Rejection of Claims 1-14 and 41 May Be Properly Withdrawn.

The wording of the pending claims has been amended to permit better comprehension of the subject matter claimed.

Applicants respectfully request that the Examiner withdraw the rejections under 35 USC § 112, second paragraph.

The 35 USC § 102(b) Rejection of Claims 1-4, 6, 7, 9, 12 and 13 Anticipated by the '336 Patent Is Urged to Be in Error.

The '336 Patent discloses a wound surface paste or sheet covering made from a reaction between dextran C (MW 40000-80000) and a bifunctional compound such as epichlorohydrin. This product is then impregnated with a humectant formulation comprising a mixture of glycerin or isopropanol/propylene gylycol and oils to hold moisture in the vicinity of the wound site. The intended uses of the '336 Patent sheet material are to reduce evaporative loss of body fluids from a wound surface, to reduce the risk of bacterial infection, and to prevent scale formation (col. 1, 1.55-65). The '336 Patent does not teach or suggest rapid blood coagulation and hemostasis at an active bleeding site.

The present invention relates to a hemostatic agent composition wherein the hemostatic agent comprises beads or grains of a crosslinked dextran. No oil-containing humectant is used because the use of oil would limit the absorbance and concentration of endogenous clotting factors and materials, this absorbance and concentration being key to the mechanism of the present invention. By high absorbance of these blood and plasma constituents and materials by the composition of the present invention, rapid blood coagulation and hemostasis occur at the active bleeding site.

In fact, Applicants urge that the '336 Patent teaches away from the present invention. The wound covering in the '336 Patent is a sheet material, rather than

insoluble beads or grains. The sheet material is designed to substantially reduce water and fluid loss at the wound site and to remove exudate from the wound site to promote healing. There is no teaching or suggestion in the '336 Patent to use the sheet material of this patent at an active bleeding site and to obtain hemostasis with this sheet material. The mechanism of action of the hemostatic polymer composition of the present invention is through high absorbance of blood and plasma constituents and materials by the crosslinked dextran beads or grains causing rapid blood coagulation and hemostasis. Such blood and plasma constituents and materials are only present in amounts useful to the present invention upon blood and/or plasma loss at active bleeding sites. Furthermore, the concentrated blood and plasma constituents are not removed from the bleeding site. Thus, Applicants respectfully urge that the '336 Patent teaches away from the present invention.

To constitute an anticipation, all the claimed elements must be found in exactly the same situation and united in the same way to perform the identical function in a single unit of the prior art. *Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc.,* 726 f.2d 724, 726, 220 U.S.P.Q. 841, 842 (Fed. Cir. 1984); *Integra LifeSciences I Ltd. v. Merck KgaA*, 1999 WL 398180, *398180, 50 U.S.P.Q.2d 1846, 1848 (S.D.Cal. 1999).

The '336 Patent fails to teach or suggest a hemostatic polymer composition comprising beads or grains of a crosslinked dextran which is useful for the rapid induction of blood coagulation and hemostasis at a bleeding site. Applicants respectfully submit that the present invention is not anticipated by the '336 Patent. Reconsideration and withdrawal of this Rejection are respectfully requested.

Claims 1-4, 6, 7, 9, 12 And 13 Are Not Anticipated by the '055 Patent.

The '055 Patent discloses a preparation for treating or cleaning a fluid-discharging surface, wound, sore, or mucous membrane. While the '055 Patent and the present application are both dextran-epichlorohydrin polymers, the consistency of the polymer in the '055 Patent may be such that high molecular weight (*e.g.*, MW 50000-270000) degradation products of fibrinogen are partly or completely excluded from the gel particles of that polymer (p. 2, l. 5-12). Thus, the concentration of both fibrin monomers and crosslinked fibrin on the actual liquid-discharging surface of the

wound can be controlled so that subsequent scar formation does not take place on that surface but at a distance therefrom (p. 1, l. 37-48). Rapid blood coagulation and hemostasis at an active bleeding site is not an intended use of the invention claimed in the '055 Patent.

In contrast, the present invention relates to a hemostatic agent and polymer composition comprising beads or grains of a crosslinked dextran molecule. The crosslinked dextran concentrates fibrinogen on the surface of the beads which in turn triggers rapid blood clotting and hemostasis directly at the active bleeding site, where such materials remain.

To constitute an anticipation, all the claimed elements must be found in exactly the same situation and united in the same way to perform the identical function in a single unit of the prior art. *Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc.,* 726 f.2d 724, 726, 220 U.S.P.Q. 841, 842 (Fed. Cir. 1984); *Integra LifeSciences I Ltd. v. Merck KgaA*, 1999 WL 398180, *398180, 50 U.S.P.Q.2d 1846, 1848 (S.D.Cal. 1999).

It is urged that the '055 Patent teaches away from the present invention. The invention in the '055 Patent causes substances excluded from the dextran epichlorohydrin polymer particles to migrate towards the outer layer of the particle mass, and therefore removes these substances from the wound. There is no disclosure in the '055 Patent directed towards application of the covering to an active bleeding site. The crosslinked dextran composition of the present invention fixes fibrinogen and other clotting factors on the surface of the polymer beads or grains to form a biodegradable clotting matrix which remains in the active bleeding site.

The '055 Patent fails to teach or suggest hemostatic composition comprising beads or grains of a crosslinked dextran useful for the rapid induction of blood coagulation and hemostasis at a bleeding site. Applicants respectfully submit that the present invention is not anticipated by the '055 Patent and urge the Examiner to withdraw this rejection.

Claims 11 and 41 Are Not Obvious Over the Combinations of References Cited by the Examiner.

Claims 11 has been rejected under 35 USC § 103(a) as allegedly being unpatentable over the '055 Patent or the '336 Patent further in view of Larson [R], or Eloy *et al.* and the '190 Patent.

Claim 41 has been rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over the '055 Patent or the '366 Patent further in view of the '653 Patent.

Both of these rejections are respectfully traversed.

The '190 Patent discloses membranes suitable as a synthetic skin substitutes wherein the membranes consists of a natural or synthetic polymer, a non-gellable polysaccharide and a cross-linking agent. The non-gellable polysaccharide is the "most critical compound" (col. 3, l. 61) and an exemplary such material is a galactomannan macromolecule. A preferred form of the '190 Patent invention and the actually claimed embodiment is a cross-linked polyacrylamide. The '190 Patent also discloses that where the natural or synthetic polymer is dextran, the dextran polymer (MW 50000-500000) is crosslinked to a nongellable polysaccharide with epichlorolydrin. The membranes of the '190 Patent are taught to act as a barrier to infection and reduce the evaporative loss of body fluids through acting as a skin substitute (col. 1, l. 1-15) and to remove exudates from the wound site (col. 9, l. 62-col. 10, 1, 2). Although passing mention is made in the specification of stopping bleeding at a wound site and acting as a hemostatic agent (col. 10, l. 48-51), rapid blood coagulation and hemostasis at a fresh, deep wound or active bleeding site is not an intended use of the invention claimed in the '190 Patent. Furthermore, the synthetic membrane of the '190 Patent is not used in the form or grains or beads. The present invention also does not utilize the required and critical non-gellable polysaccharide component of the '190 Patent.

It is respectfully urged that the '190 Patent fails to remedy the deficiencies of the primary references.

As for Larson or Eloy *et al.,* assuming *arguendo* that these references teach what the Examiner alleges, these citations do not teach or suggest the use of crosslinked dextran beads or grains as a hemostatic agent. This is the main disability and failing of the '055 and the '366 Patents.

As for the '653 Patent, as it has been applied to present claim 41, Applicants urge that this Patent does not teach or suggest the present invention. As noted above, the '055 and '336 Patents fail to teach or suggest the use of beads or grains of a crosslinked dextran in the staunching of blood at a bleeding site. The '653 Patent teaches only wound dressings and does not at all relate to hemostasis.

Reconsideration and withdrawal of the § 103 Rejections of claims 11 and 41 are requested.

There Is No Suggestion to Combine Any of the References.

Finally, there is no suggestion in any of the aforementioned references to combine their disclosures in a manner which discloses either the compositions or methods of use of the compositions claimed in the present invention. Applicants urge that any possible combination set forth by the Examiner would not comprise the elements of the claimed invention and would be improper because the references taken alone or together do not teach or suggest the present invention. Such a combination is proper only when there is some objective teaching in the prior art that would lead one of ordinary skill in the art to combine the relevant teachings of the references. *In re Fine*, 5 U.S.P.Q. 2d 1956, 1598 (Fed. Cir. 1988)

CONCLUSION

For all the above reasons, Applicants respectfully request the Examiner to withdraw all objections to and rejections of the present invention. It is urged that this application is now in condition for allowance. Early and favorable action by the Examiner is earnestly solicited.

Respectfully Submitted,

Date 8/1/01

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SPECIFICATION AS AMENDED

Page 1, Paragraph 1, **delet** this paragraph in its entirety:

[This application claims priority of provisional application No. 60/108,185, filed November 12, 1998 and pending application Serial No. 09/290,846, Filed April 13, 1999, each of which is incorporated by reference herein].

And **replace** with the following paragraph:

This Application claims priority of Provisional Application No. 60/108,185, filed November 12, 1998 and is a Continuation-in-Part of co-pending Application Serial No. 09/290,846, filed April 13, 1999, each of which is incorporated by reference herein.

Page 21, Paragraph 1, **delete** this paragraph in its entirety:

[Suitable hydroxyl group-containing substances are: polyvinyl alcohol sugar alcohol's, carbohydrates (i.e. saccharose, sorbitol), polysacccharides, (i.e dextran, starch, alginate, cellulose), and hydroxyl group containing neutral derivatives of the above compounds].

And **replace** with the following paragraph:

Suitable hydrol group-containing substances are : polyvinyl alcohol, sugar alcohols, carbohydrates (*i.e.*, saccaharose, sorbitol), polysaccharides (*i.e.*, dextran, starch, alginate, cellulose), and hydroxyl group containing neutral derivatives of the above compounds.

Page 21, Paragraph 2, **delete** this paragraph in its entirety:

[Examples of suitable bifunctional organic substances for preparing the hemostatic polymer composition of the invention include one of epichlorohydrin, dicholorhydrin,

diepoxyburan, disepoxypropyl ether, ethylene-glyco-bis-epoxypropy ether].

And **replace** with the following paragraph:

Examples of suitable bifunctional organic substances for preparing the hemostatic polymer composition of the invention include one of epichlorohydrin, dicholorhydrin, diepoxybutane, diepoxypropyl ether, ethylene-glycol-bis-epoxypropul-ether.

CLAIMS AS AMENDED

Please **amend** claims 1, 3, 9, 11, 12, 13, 24, 26, 33, 37, and 41 to read as follows:

1. (Amended) A dry, storage stable, sterile [wound] dressing for application to a bleeding site which [provides] comprises a dry hemostatic zone, said [dressing] zone comprising a matrix containing hemostatis-promoting amount of a hemostatic agent which accelerates blood coagulation and clot formation at an interface between [a wound surface] the bleeding site and the hemostatic zone wherein said hemostatic agent comprises beads or grains of crosslinked dextran.

3. (Amended) The dry, sterile, [removable wound] dressing according to claim 1, further comprising a substrate [and the wound dressing according to claim 1].

9. (Amended) The [wound] dressing of claim 1, wherein [the substance containing the halogen atom] the dextran is crosslinked with epichi[l]lorohydrin [or dichlorohydrin].

11. (Amended) The [wound] dressing according to claim 1, wherein the hemostatic [polymer composition] agent further contains at least one of collagen, fibrinogen and thrombin.

12. (Amended) The [wound] dressing according to claim 1, [further comprising] wherein the matrix further comprises a pharmaceutical agent.

13. (Amended) The [wound] dressing according to claim 12, wherein said pharmaceutical agent is at least one of anti-inflammatory analgesic agents, steroidal anti-inflammatory agents, antihistamines, local anesthetics, bactericides or disinfectants, vasconstrictors, chermotherapeutic drugs, antibiotics, keratolytics,

cauterizing agents, antivirual drugs and mixtures thereof.

24. (Amended) A dry, sterile [wound] dressing for application to a bleeding site which provides an anti-microbial hemostatic zone, said zone [dressing] comprising a matrix containing a complex comprising a hemostatis-promoting amount of a hemostatic agent effective to accelerate blood coagulation and clot formation at an interface between [a wound or] the bleeding site surface and the reagent zone and an effective amount of anti-microbial agent wherein said hemostatic agent comprises beads or grains of crosslinked dextran.

26. (Amended) A hemostatic patch suitable for rapidly arresting bleeding and inducing rapid clot formation at a [wound or] bleeding site, said patch comprising a dry sterile storage stable flexible matrix containing a hemostatic agent composition on one face only thereof which provides a dry hemostatic zone, said patch being effective to accelerate blood coagulation and clot formulation at an interface between a [wound or] bleeding site surface and the reagent zone of the patch, wherein said hemostatic agent comprises beads or grains of crosslinked dextran.

33. (Amended) A method for staunching bleeding from a [wound] bleeding site, which comprises applying to the bleeding site [a wounded surface of the wound] the hemostatic patch according the hemostatic patch according to claim 26 for a period of time sufficient to staunch said bleeding.

37. (Amended) A bandage for application to a bleeding site comprising

(i) a central portion adapted to be directly applied to the [wounded] bleeding site; and

(ii) a strip for adhesion to an area continuous to and in spaced-apart relation to the [wound or] bleeding site, whereby the bandage is adapted to be applied substantially, without wrinkling to a contoured or flexing body part and is adapted to adhere reliably, wherein the central portion of said bandage comprises a hemostatic zone containing a suitable matrix having a hemostasis-promoting amount of a hemostatic agent effective to accelerate blood coagulation and clot formation in an interface between a [wound or] bleeding site surface and the central portion of said bandage wherein said hemostatic agent comprises a central portion adapted to be directly applied to the bleeding site and wherein said hemostatic agent comprises beads or grains of crosslinked dextran.

41. (Amended) A dry, [wound] removable dressing pouch comprising

(a) a strip comprising:

(i) a flexible substrate sheet and the dry sterile [wound or] dressing of claim 1 carried on said strip and

(ii) a protective layer enclosing the strip.

Please **add** the following new claims:

45. A pharmaceutical composition useful for rapid induction of blood coagulation and homeostasis comprising a therapeutically effective amount of a hemostatic polymer in combination with a pharmaceutically acceptable carrier or diluent, said hemostatic polymer comprising beads or grains of a crosslinked dextran.

46. The pharmaceutical composition according to claim 45, wherein the aerosol suspension includes at least one of a CO_2, nitrogen, air.

47. The pharmaceutical composition according to claim 45, wherein the said homeostatic polymer composition is a powder.

48. The pharmaceutical composition according to claim 45, wherein the homeostatic polymer composition is a microsphere.

49. The pharmaceutical composition according to claim 45, wherein the dextran is crosslinked with epichlorohydrin.

50. The pharmaceutical composition according to claim 45, further comprising a bioactive agent.

51. The pharmaceutical composition according to claim 50, wherein the bioactive agent is one of antibodies, antigens, antibiotics, wound sterilization substances, thrombin, blood clotting factors, chemo-therapeutic drugs, gene therapy agents or combinations thereof.

52. The pharmaceutical composition according to claim 50, wherein the bioactive agent comprises a diagnostic marker.

53. The pharmaceutical composition according to claim 45, further comprising collagent, fibrinogen or thrombin.

54. A bandage or dressing for inducing rapid blood coagulation and homeostasis comprising a therapeutically effective amount of a hemostatic polymer comprising beads or grains of a crosslinked dextran.

55. A foam product useful for inducing rapid blood coagulation and

homeostasis comprising a therapeutically effective amount of a hemostatic polymer comprising beads or grains of a crosslinked dextran.

56. A dressing for inducing rapid blood coagulation and homeostasis comprising a therapeutically effective amount of a hemostatic polymer comprising beads or grains of a crosslinked dextran.

57. A dressing according to claim 56 in the form of a gel.

58. A blood coagulating composition comprising a hemostatic polymer in combination with a pharmaceutically acceptable carrier or diluent, the hemostatic polymer comprising beads or grains of a crosslinked dextran.